Alternative Methods for Assessment of Split Renal Function

HENRIK BJÖRKMANN
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Abstract

Living kidney donation is a clinical situation with unique features in the sense that healthy individuals voluntarily expose themselves to certain risks and inconveniences. Therefore, eliminating as much of the associated discomfort as possible is crucial. The primary aim of this study was to evaluate whether it is possible to use the examination with computed tomography (CT), which is essential to the investigation, also for determining the ratio of the two kidneys’ function – the split renal function. If possible, an examination with gamma camera renography could be excluded from the work-up.

To investigate this possibility, 27 subjects who had underwent CT and renography as part of kidney donor investigation were studied retrospectively. The quantity of contrast material in each kidney was considered proportional to that kidney’s function, and measurement was made in each of the two available contrast phases. The results were compared to the results from renography. A similar analysis was conducted in 38 patients investigated for suspected renal artery stenosis with CT and renography, including a study of an automatized method for the acquisition of data from CT. For further scrutiny, a respiratory triggered dynamic contrast-enhanced magnetic resonance imaging (MRI) examination was investigated in 26 individuals. Results of split renal function were compared with renography and with CT in a subgroup. To study the possibility of facilitating the data analysis with CT, a formula for approximation of the contrast attenuation was studied in 64 subjects. An analysis of the significance of choice of contrast phase was also conducted in 43 subjects.

Unsatisfactory agreement with renography resulted from the CT analysis of previous donors, partly due to technical shortcomings. However, the technique was recognized to have a potential value. In the subsequent material, the settings were improved, with beneficial effects on the agreement. Respiratory-triggered MRI generated high quality examinations of renal uptake and excretion, with results harmonizing well with renography and CT. The approximation formula applied to CT resulted in higher accuracy for renal volume assessment than with the automatic method, and an acceptable agreement of the split renal function estimate.

From the presented results, a revision of the current donor investigation protocol is suggested. CT gives sufficient information to exclude renography as a routine examination. In cases of uncertainty, renography is recommended for secondary evaluation.

Keywords: Split renal function, Live kidney donor, CT, Renography, Dynamic MRI, Renal volume, Respiratory triggering

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urn:nbn:se:uu:diva-8513 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-8513)
To Johanna

Granska mig, Herre, och pröva mig, rannsaka hjärta och njurar!
Ps. 26:2
List of papers

This thesis is based on the following studies, which will be referred to in the text by their Roman numerals


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## Abbreviations

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<th>Description</th>
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<tr>
<td>ACE</td>
<td>Angiotensin converting enzyme</td>
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<tr>
<td>CAPD</td>
<td>Chronic ambulatory peritoneal dialysis</td>
</tr>
<tr>
<td>CT, -A</td>
<td>Computed tomography, -angiography</td>
</tr>
<tr>
<td>DSA</td>
<td>Digital subtraction angiography</td>
</tr>
<tr>
<td>DTPA</td>
<td>Diethylenetriaminepentaacetate</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
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<tr>
<td>HU</td>
<td>Hounsfield units</td>
</tr>
<tr>
<td>IVP</td>
<td>Intravenous pyelography</td>
</tr>
<tr>
<td>MAG3</td>
<td>Mercaptoacetyltriglycine</td>
</tr>
<tr>
<td>MDCT</td>
<td>Multi detector computed tomography</td>
</tr>
<tr>
<td>MR, -A, -I</td>
<td>Magnetic resonance, -angiography, -imaging</td>
</tr>
<tr>
<td>NFP</td>
<td>Net filtration pressure</td>
</tr>
<tr>
<td>RAAS</td>
<td>Renin-angiotensin-aldosterone system</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of interest</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasonography</td>
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<tr>
<td>VOI</td>
<td>Volume of interest</td>
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Introduction

The most common causes of chronic renal failure in a Swedish panorama are chronic glomerulonephritis, diabetes mellitus, chronic pyelonephritis, nephrosclerosis and hereditary polycystic kidney disease. In a state of progressive renal damage, the kidneys’ functional units – the nephrons – have the ability to function relatively normal for long time. However, when they are finally terminated one by one and the capacity goes down to around 25% of the original, a vicious circle is initiated whereby the remaining nephrons undergo compensatory changes, which in the long run also lead to their termination. The kidneys are silent organs and the residual capacity is substantial from the beginning, implying that symptoms of renal failure often do not appear until less than 15 or 20% of the original function remains. The clinical syndrome of renal failure is known as uremia, the symptoms of which include e.g fatigue, thirst, polyuria, edema, nausea, diarrhea, anemia, osteoporosis and hypertension. All of these symptoms reflect different aspects of the kidneys’ normal function.

Two principal treatment options exist for an individual who has reached end-stage renal failure, when dietary treatment is insufficient for preventing uremic symptoms: dialysis or transplantation. Both of these alternatives can be divided into subgroups. Chronic ambulatory peritoneal dialysis (CAPD), which utilises peritoneum as a membrane for filtration, is an option for patients with some remaining renal function, who have the ability to cooperate towards the specific demands of the therapy. However, a minority of all dialysis patients applies this method, and between 70 and 80% of the approximately 2800 people in Sweden who are subject to active uremia treatment instead undergo intermittent hemodialysis. This involves extracorporeal circulation with filtration through an external filter and is a more efficient method than CAPD, but is associated with more limitations in terms of time consumption and lifestyle restrictions.

Although both dialysis methods are life-supporting for many people, the side effects are discouraging and the life expectancy is dramatically reduced, with a median survival of less than three years after initiated treatment [1]. For patients who qualify for surgery, the best option in end-stage renal failure is renal transplantation, both with regards to subjective experience and survival [2] and health economical aspects. The first renal transplantation in Sweden was performed in 1964 and since then, approximately 11 000 transplantations have followed [3]. From originally disappointing long-term results, the estimated rate of functioning transplants after five years with current immunosuppressive therapy is 75% [3].
The improving results have led to increased demands for transplantation among patients with end-stage renal failure, not possible to satisfy with the number of cadaveric organs available. Furthermore, the quantity of organs from deceased donors is decreasing. The importance as well as the number of living renal donations therefore is increasing in a worldwide perspective. For natural reasons, living donation is the better alternative as the surgical procedure can be performed electively under ideally prepared conditions. This is reflected in an observable survival benefit, compared with cadaveric kidneys [4]. Donation from a first-degree relative (parent or sibling) has had the best results, but with modern immunological methods, HLA (human leukocyte antigen) or ABO (blood group) incompatibility is no contraindication [5-7]. A different approach sometimes applied to gain immunological match is a crosswise donation between two recipient-donor couples. Occasional suggestions of commercializing the organ market have not had much impact in a Swedish panorama and would be a vast departure from the ethical principles of organ donation.

The living renal donor is a healthy volunteer, one of few clients in the healthcare system that does not qualify to be denoted as a “patient”. In a regular patient context, the risks associated with any diagnostic or therapeutic action considered can and must be weighed against their benefits in the present situation, to ensure the safety of the patient. However, for the living renal donor, no direct personal benefits are at hand, other than the extensive medical check-up included in the procedure. The risks and inconveniences are still present, and consequently, it is an eager task to minimize those risks as far as possible. One important step towards this has been the introduction of a laparoscopic surgical technique for harvesting the donor kidney [8], and subsequently the hand-assisted retroperitoneal approach [9], which has decreased the postoperative morbidity [10]. It deserves mentioning that the life expectancy after living renal donation has been reported higher than in a age-matched control group [11], which is likely to depend on a selection bias of healthy individuals for donation. Whether altruism itself prolongs life would be more speculative to claim.
Imaging is a crucial part of the preoperative planning of the potential donor, and especially with the minimally invasive techniques, the importance of correct description of the anatomical conditions beforehand has increased. Previously, to give a proper mapping of the different aspects of the renal anatomy, digital subtraction angiography (DSA) was required for vascular depiction, intravenous pyelography (IVP) for qualitative function assessment and characterization of the outflow system, ultrasonography (US) and computed tomography (CT) for evaluation of the parenchyma, and renography for quantification of the relative contribution of each kidney to the total renal function – often referred to as “split renal function”. The latter is important information when it comes to the selection of which kidney to donate. In case of symmetrical function and morphology, the left kidney is usually preferred because of vascular conditions more convenient for reimplantation. Sometimes, however, anatomical variants such as duplication, polar arteries etc make the right kidney more favourable. If one of the kidneys has a notably lower proportion of the total function, this also must be considered. The most crucial issue is not to leave the donor with a single, poorly functioning kidney, but the worth of transplanting such a kidney also needs to be reflected on.

During the past ten years, the development of imaging methods has improved the diagnostic accuracy while minimizing the inconvenience for the donor. The result has been a simplified protocol for donor investigation, so that at our institution, a single examination with multidetector computed tomography (MDCT) has replaced both the traditional IVP and the invasive DSA. US remains for practical reasons as an initial screening method which may identify gross anatomical conditions that disqualify from further efforts. Renography still is required for the purpose of calculating split renal function, but is a method with few other indications. The theoretical possibility of calculating split renal function from a contrast enhanced CT examination has long been recognized. If this would prove feasible, the perspective is to further condense the preoperative investigation procedure and make CT the only essential technique, for the benefit of the potential donor. To analyse whether this is possible, and how it can be accomplished in the most practical way, were the general aims of this project.
Anatomy of the kidneys

The kidney (Figure 1) is a paired organ (which is, by the way, the very prerequisite of this study) located retroperitoneally, each kidney on either side of the vertebral column. The right kidney is most often slightly more caudally placed than the left one, as the liver is situated directly superior to it. Each kidney has a weight of about 150 g, with average measures of 11 cm × 5 cm × 3 cm (length × width × thickness). On the medial side, the kidney has an opening, the hilum, where the renal artery enters and the renal vein and ureter leaves the kidney. The inner, fat-containing part of the kidney is called the renal sinus. A fibrous capsule surrounds each kidney, which is further protected by a layer of perirenal fat and a thin layer of connective tissue known as Gerota’s fascia.

The parenchyma of the kidney is divided into the cortex (outer portion) and the medulla (inner portion). The medulla is arranged in renal pyramids, cone shaped structures with the base facing the cortex and the tip of the pyramid, called renal papilla, directed towards the renal sinus. Between the renal pyramids, the cortex extends inwards to the sinus, with these extensions known as renal columns.

The functional unit of the kidney is the nephron (Figure 2), of which each kidney has approximately 1.2 million at birth. Each nephron consists of a number of parts: the renal corpuscle made up of the glomerulus and Bowman’s capsule, the proximal tubule, the loop of Henle and the distal tubule. The glomerulus is a ball of capillaries, surrounded by the double-walled Bowman’s capsule continuing into the proximal tubule. The corpuscle and the proximal tubule are located in the cortex, whereas the loop of Henle extends into the medulla and then returns to the cortex, where the distal tubule passes adjacent to the glomerulus.

The distal tubules end into collecting ducts, which transport the urine and converge in the renal papilla into a minor calyx. Several minor calyces form a major calyx, of which there are two or three in each kidney. They, in turn, converge into the renal pelvis located in the renal sinus. The pelvis continues to the narrower ureter which leaves the kidney through the hilum and transports the urine to the urinary bladder.

The renal artery, which branches directly from the aorta, enters the kidney through the hilum, as mentioned. It divides into segmental arteries and successively into interlobar arteries, which run within the renal columns to reach the cortex. Branches from the interlobar arteries form arcuate arteries, oriented parallel with the base of the renal pyramid, and from these, the interlobular arteries supply the cortex. Despite their name, the arcuate arteries do not form a system of collateral arterial blood flow, and the nephrons are supplied by functional end arteries. The interlobular arteries continue to branch into the afferent
Figure 1.
The kidney.
arterioles, entering the glomerulus as capillaries and returning in the shape of efferent arterioles. The efferent arterioles branch again into a second web of capillaries, surrounding the tubules. Subsets of these capillaries follow along the loop of Henle through the medulla as vasa recta. Ultimately, the venous drainage runs parallel to the arterial supply, in the successive forms of interlobular, arcuate and interlobar veins. The latter ones converge into the renal vein, which connects to the inferior vena cava.

Figure 2.
The principal parts of the nephron, the functional unit of the kidney. In this illustration, the nephron has been unfolded, whereas normally the distal tubule passes adjacent to the glomerulus.
Definition of renal function

Several homeostatic processes and functions are monitored and intricately regulated by the kidneys. The concept of “renal function” must therefore be defined in order to discuss the measurement of it. Five major tasks handled by the kidneys can be pointed out:

1. **Regulation of water and electrolyte balance**

   This is the macroscopically most evident function handled by the kidneys. We drink, and therefore we urinate. Or conversely, we urinate, and therefore we drink. The kidneys can regulate the excretion of water and minerals independently to match great variations in intake. Regulation of acid-base balance is an important component of the electrolyte balance control.

2. **Excretion of waste products**

   The kidneys share the task of clearing the body from waste products from metabolic processes and foreign substances such as drugs mainly with the liver. A quantitatively bigger proportion of this duty is conducted by the liver, but the clearance of particularly nitrogen-containing metabolic by-products cannot be overtaken by any other organ than the kidneys.

3. **Regulation of the blood pressure**

   Since the arterial blood pressure is dependent on the circulating blood volume, one aspect of the kidneys’ methods to maintain the blood pressure is by regulating the water balance, as commented on above. More mechanisms are also involved. In response to a decrease in blood pressure, the secretion of the hormone renin from the kidneys is increased. The effect of renin is to increase the formation of the active hormone angiotensin II, which is a potent vasoconstrictor itself, and further has the effect of increasing the sympathetic tone and the aldosterone secretion from the adrenal cortex. Aldosterone increases the reabsorption of Na\(^+\) ions from the renal tubules, and thus increases extracellular osmolality. This leads to increased antidiuretic hormone (ADH) secretion from the posterior pituitary, with the effect of increasing the reabsorption of water in the distal tubules and collecting systems of the nephrons. The increased fluid volume contributes in raising the blood pressure. The system involving these processes is generally abbreviated RAAS (renin-angiotensin-aldosterone system) (Figure 3).
4. Regulation of the level of red blood cells

Stimulated by a decrease of partial oxygen pressure in the blood, as seen e.g. in anemia or in staying on high altitudes, the kidneys secrete the hormone erythropoietin, which in turn stimulates the bone marrow to increase the production rate of red blood cells.

5. Calcium regulation

Vitamin D3 is formed in the skin and undergoes activation in two steps: first by conversion into 25-hydroxycholecalciferol in the liver, followed by conversion into the active compound 1,25-dihydroxycholecalciferol in the kidneys. Parathyroid hormone is secreted in response to lowered levels of extracellular Ca$^{2+}$ ions, and is required for the renal activation of vitamin D. The active form of vitamin D exerts its effects by increasing the intestinal uptake and renal reabsorption of Ca$^{2+}$ ions, and by stimulating the bone osteoclast activity.
It can be recognized that the each of the symptoms and signs previously mentioned associated with end-stage renal failure is, more or less directly, correlated with these different aspects of renal function. The accumulation of metabolic waste products which are toxic in high concentrations accounts for the uremic syndrome, and the adequate clearance of substances via urine is what logically represents renal function as a measurable, distinct property.

Urine formation

Three principal processes in the nephron account for the composition of urine: filtration, reabsorption and secretion. The processes balance each other to match the exact needs of excretion or retention of individual substances.

Filtration

Filtration is the process occurring in the renal corpuscle, when fluid is passively transported from the glomerular capillaries to Bowman’s capsule. The membrane is composed of fenestrated glomerular capillary endothelium, a basement membrane and the podocyte cells that constitute the visceral layer of Bowman’s capsule. The membrane has properties of pore size and charge that allow water and small solutes to pass freely, but prevents larger proteins from being filtered. The filtration is driven by the filtration pressure, i.e., the net gradient over the membrane composed of the pressure gradient from the differences in hydrostatic and colloid osmotic pressures in the two compartments, typically around 10 mmHg.

The degree of filtration in the glomeruli is determined by two properties, the renal plasma flow and the filtration fraction. The kidneys receive an exceptionally high proportion of the cardiac output, much higher than the metabolic needs of the organs themselves. Under normal conditions, approximately 20% of the total blood flow enters the kidneys, or about 1200 mL/min in an average size male. The internal distribution in the kidneys results in the cortex receiving more than 90% of the renal blood flow. The purpose of this high blood flow is to produce large volumes of filtrate as a condition for the careful regulation of the substances to be excreted or retained. The renal plasma flow accounts for the proportion of the blood flow representing the proportion of plasma in blood, typically 55%, and consequently $1200 \times 0.55 = 660$ mL/min. An average filtration fraction of 20% results in a glomerular filtration rate (GFR) of $660 \times 0.20 = 132$ mL/min. With 125 mL/min as a standard value of glomerular filtration rate, 180 L of filtrate, or primary urine, is produced every day.
Reabsorption and secretion

From Bowman's capsule, the primary urine flows through the remaining parts of the nephron: the proximal tubule, the loop of Henle, the distal tubule and into the collecting duct. From the “raw material” of the filtrate, the majority of electrolytes, water and organic substances are reabsorbed in the tubules. Different mechanisms such as passive diffusion, active reabsorption or secondary active reabsorption account for the uptake in different parts of the tubules. Several substances, both metabolic by-products and foreign compounds, also utilize a mechanism of active or passive tubular secretion for their clearance. Only in the order of 1% of the filtrate remains as urine when it has passed through the collecting ducts to the papillae.

Measurement of renal function

Different principles are applied for directly or indirectly measuring the function of clearing the organism from substances through the urine. To quantify the efficiency of the kidneys’ ability to fulfil their task of excreting a harmful substance or waste product, the clearance for the specific substance can be derived. Clearance is defined, with a somewhat theoretical concept, as the amount of plasma which is completely cleared from the substance per minute, and is calculated with the equation:

\[ V_{\text{cleared}} = V_u \cdot \frac{C_u}{C_p} \]

where \( V_{\text{cleared}} \) = clearance (mL/min), \( V_u \) = urine production (mL/min), \( C_u \) = concentration in urine (mg/mL) and \( C_p \) = concentration in plasma (mg/mL).

The mechanism by which a substance is cleared by the kidneys will determine which physiological process that is reflected by its clearance value. As the glomerular filtration is essential for all other excretory processes, it is specifically interesting to measure renal function in terms of GFR. The original concept for determination of renal clearance included measurement of the endogenous substance creatinine [12]. Creatinine is formed in the body as a degradation product of muscle cells and is mostly cleared by glomerular filtration and to a lesser extent by active tubular secretion. The creatinine clearance is calculated based on the clearance equation above, or approximated according to formulas such as the Cockcroft-Gault [13] or the Modification of Diet in Renal Disease (MDRD) [14] equations. For everyday purposes, the most common practice is to use the plasma or serum level of creatinine as an indirect measure of its clearance. However, the concentration of creatinine depends on multiple factors such as age, sex, body weight, physical activity and diet, and is insensitive to moderately
decreased renal function. An endogenous substance more recently introduced for GFR estimate from a single blood sample, is cystatin C [15]. Independent of muscle mass or gender, cystatin C is considered an advantageous alternative to creatinine, with higher accuracy reported [16].

Classically, the gold standard for GFR assessment involved measuring the clearance of the exogenous polysaccharide inulin. Inulin has the properties of being freely filtered in the glomerulus, not being reabsorbed or secreted in the tubule, and not being produced or metabolized in the kidney. Hence, inulin is an ideal filtration marker and its clearance will be equal to the GFR. As inulin clearance is expensive and time-consuming to perform, more convenient filtration markers have been developed. These include e.g. the radioactively labelled marker $^{51}$Cr-EDTA or the iodinated contrast medium iohexol [17], the latter of which in recent decades has become the most widely used substance for GFR measurement in a Swedish panorama. The inconvenience of urine collection and the associated difficulty in obtaining exact values has led to development of methods which only require blood sampling. From e.g. four samples at different time points after intravenous injection of a filtration marker, the curve of plasma concentration is extrapolated and the clearance is calculated as the injected amount of marker divided by the area under the time-concentration curve. This is often referred to as plasma clearance. For routine use and unless particularly high precision is needed, the method can be further simplified to include only one blood sample.

**Measurement of split renal function**

Assessment of GFR is an integral part of a comprehensive investigation of renal function in general and, specifically, in the renal donor investigation. However, with the settings described above, the GFR value will represent both kidneys’ total function and not reveal the internal function ratio. Theoretically, the measurement of urine concentration and volume could be modified to include selective urine collection via ureter catheters, but this is not considered acceptable in an everyday clinical setting due to its invasiveness. For assessment of split renal function, radionuclide methods have long been the routine. Initially, simple scintillation detectors were used to count the uptake of radioactive tracers in each kidney, but today, the gamma camera is used for quantification and visualisation. The radioactive tracers and carrier molecules have also been subject to evolution. A high extraction fraction in the kidneys is the key property to obtain images with an ideal signal-to-noise ratio. Radioiodine labelled hippurate has a high extraction fraction, but $^{123}$I-OIH (orthoiodohippurate) has limited availability and $^{131}$-I-OIH(159,457),(186,491) produces noisy gamma camera images due to high photon energy. Today, technetium, $^{99m}$Tc, is the most frequently used isotope due to excellent physical properties and high availability. The compound $^{99m}$Tc-
DTPA was originally used but has since the mid 1980’s been gradually replaced by \(^{99m}\text{Tc-MAG3}\). Compared to DTPA, MAG3 has a higher extraction fraction, approximately 68\% [18], which is largely attributed to tubular secretion. This implies high quality of the gamma camera image – the renogram – but also means that a different physiological property is assessed than with the filtration markers previously discussed.

Various algorithms for processing of the raw material from the gamma camera are used. The slope of the uptake curve or the integral in specified time intervals are principles sometimes applied. However, the most widespread method probably is the Patlak, or Patlak-Rutland, plot, which was derived theoretically by Patlak and Rutland separately [19-21]. As a graphical model for – in its simplest form – analysis of the unidirectional transport of a tracer from one compartment to another, it has been recognized useful for determination of renal clearance. Specifically, for split renal function calculation, the Patlak-Rutland plot has proven to be a robust model [22].

To apply the Patlak-Rutland plot, a plasma input curve and background-corrected uptake curves over each kidney are obtained. The plot is then derived as follows [23]. During the phase of uptake of tracer in the kidneys, the uptake rate is proportional to the plasma concentration, i.e.

\[
\frac{dK(t)}{dt} = C \cdot P(t)
\]

where \(K(t)\) is the concentration in the kidney, \(C\) the constant of proportionality equal to the clearance, and \(P(t)\) the plasma concentration. Integrating the equation results in

\[
K(t) = C \cdot \int P(t) dt
\]

Dividing both sides of the equation by \(P(t)\) renders the ultimate equation of the Patlak-Rutland plot,

\[
\frac{K(t)}{P(t)} = C \cdot \frac{\int P(t) dt}{P(t)}
\]
A straight line with the slope $C$ is obtained when plotting these variables in a graph, representing the clearance of the tracer. The processing steps from the first equation are a way of eliminating the effects of the blood background. If either of the first two equations (which would also represent straight lines with the slope $C$) were to be used, it can be inferred that alterations in the amount of blood background will affect the slope to be non-equal to the clearance.

**CT measurement of split renal function**

One of the earliest proposals addressing this issue, from Dawson and Peters [24], simply included application of the Rutland-Patlak plot with CT. Actually, two different methods were introduced, although one of them, called “delayed CT” was of less value for this discussion. That method was similar to the regularly used principle of plasma clearance measurement: the concentration of the contrast medium iohexol was measured 2, 3 and 4 hours after intravenous injection for contrast-enhanced CT, and the clearance was calculated from the extrapolated curve. However, instead of obtaining the concentration measurements via blood sampling, this was accomplished by scanning on a single abdominal level and measuring the attenuation value in the psoas muscle. Hence, that method was only useful for assessing the global renal function, the GFR.

The second method was denoted “dynamic CT” and provided a model for calculation of each kidney’s function. After intravenous bolus injection of iohexol, a single section including both kidneys was repeatedly examined with 5 second intervals for 2 minutes. The resulting values of mean attenuation of each kidney were used to generate a signal-time curve illustrating the perfusion and parenchymal uptake, to which the Patlak-Rutland plot was then applied. Despite its elegance, the authors recognized the difficulties in transferring the method to a routine practice, for some reasons. The calculated result represents GFR per volume unit of renal parenchyma, which may be an interesting concept in theory, but needs to be completed with assessment of the volume of each kidney to be practically valuable. Hence, additional scanning of the entire kidneys needs to be done after the dynamic scanning. Regional inhomogeneities in parenchymal contrast uptake, which is one of the risks associated with the algorithm, are then likely to be detected – although not easily corrected for. Motion of the patient on the table, and of the kidneys during respiration, may result in an inconsistent scanning plane, causing an error to the signal-time curve. However, the main objection to the model probably is the extra radiation exposure and contrast material dose required, which is of varying importance depending on the clinical setting. The model has been re-evaluated by other authors [25] and found to be reliable. It thus illustrates the potential of CT for split renal function measurement, but also highlights the negative aspects to be considered.
An algorithm which in the present context seemed more feasible was suggested a few years later by Frennby et al [26]. Their method was based on the recognition that the total amount of contrast material in the kidney at one time-point, before any of it has been excreted, should be proportional to the kidney’s capacity for contrast medium uptake, i.e. glomerular filtration. The algorithm included manual ROI drawing in all individual CT images and noting the values of mean attenuation and area. From there, the total attenuation value contributed by contrast medium in each kidney was calculated and assumed proportional to that kidney’s relative function. In the comparison with $^{99m}$Tc-DTPA renography, the theory met the expectations and demonstrated good agreement. By the same authors, the method later proved to have high intra-subject repeatability [27], and different authors recently gained similar close agreement [28]. However, with a seemingly analogous algorithm, poorer agreement has also been reported [29], leading to some doubt regarding the robustness of the technique.

The hard-working group which in recent years have made the most interesting attempts to develop useful physiologically derived models applied to extended routine protocols are Hackstein et al [30-33]. The key feature in their work, denoted the “Two-point Patlak plot”, has been repeatedly evaluated and fine-tuned. As a starting point, a standard CT examination with scanning unenhanced and in corticomedullary and nephrographic contrast phase was used. In addition to the existing image material, the aorta attenuation was measured in the images obtained from the bolus triggering scans, and from an extra set of low-dose scans between the two contrast phases. This would generate a nearly complete plasma input curve useful for a Patlak-Rutland plot. To obtain a renal uptake curve, however, only the two points available from the respective contrast-enhanced scans were used. Despite a thoroughly derived model, some uncertainty may therefore still exist concerning the interpolation of a renal attenuation curve from the arterial peak to a point representing the parenchymal uptake. The method for evaluation has mostly comprised a comparison of the sum of “single-kidney GFR” of both kidneys with plasma clearance as a reference, not evaluating the results of split renal function. However, in the most recent publication [31], the model was revised to only include assessment of split renal function, which was compared to gamma camera renography.

An overview of the different methods proposed for split renal function estimation from CT is given in Table 1, with results compared with reference methods and advantages and disadvantages briefly stated. Evaluation of the accuracy of each method is in some instances complicated by inadequate presentation of the results. As the present study started with a retrospective analysis of previous donors, it was apparent that a method based on an existing routine examination was initially required.
Table 1.
Overview of previous reports of CT for measurement of split renal function. LA, limits of agreement.

<table>
<thead>
<tr>
<th>Author</th>
<th>Equipment</th>
<th>Principle</th>
<th>Algorithm</th>
<th>Reference</th>
<th>Results</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>Dawson, 1993 [24]</td>
<td>Conventional CT</td>
<td>Repeated scanning in fixed section</td>
<td>Patlak-Rutland plot</td>
<td>N/A</td>
<td>GFR per cm³ 0.41 mL/min</td>
<td>Dynamic study</td>
<td>Radiation dose, risk of regional inhomogeneity and breathing error</td>
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<tr>
<td>Frennby, 1995 [26]</td>
<td>Conventional CT</td>
<td>Static scanning in two directions</td>
<td>Whole kidney attenuation</td>
<td>⁹⁹ᵐTc-DTPA renography</td>
<td>r = 0.98</td>
<td>Potentially simple principle</td>
<td>Complicated protocol due to technical limitations</td>
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<tr>
<td>Frennby, 2001 [27]</td>
<td>Single detector spiral CT</td>
<td>Routine scanning in nephrographic phase</td>
<td>Whole kidney attenuation</td>
<td>Intra-subject reproducibility</td>
<td>r = 0.99</td>
<td>Convenient routine protocol</td>
<td>Comparison with reference protocol</td>
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<tr>
<td>Hackstein, 2001 [30]</td>
<td>Single detector spiral CT</td>
<td>4-phase scanning</td>
<td>“Two-point Patlak plot”</td>
<td>Radionuclide renography</td>
<td>y = 0.58x + 18.6, r = 0.90</td>
<td>Efficient use of available data</td>
<td>Several assumptions and interpolations required</td>
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<tr>
<td>Tsushima, 2001 [25]</td>
<td>Not stated</td>
<td>Repeated scanning in fixed section</td>
<td>Patlak-Rutland plot</td>
<td>⁹⁹ᵐTc-DTPA renography</td>
<td>95 % LA: -8.7–6.9 % points</td>
<td>Dynamic study</td>
<td>Radiation dose, risk of regional inhomogeneity and breathing error</td>
</tr>
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<td>El-Diasty, 2004 [29]</td>
<td>MDCT</td>
<td>Routine scanning in nephrographic phase</td>
<td>Whole kidney attenuation, GFR calculation</td>
<td>⁹⁹ᵐTc-MAG3 renography</td>
<td>r = 0.54</td>
<td>Convenient routine protocol</td>
<td>GFR calculation factor not theoretically derived</td>
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<tr>
<td>Fowler, 2006 [28]</td>
<td>16-detector MDCT</td>
<td>Routine scanning in nephrographic phase</td>
<td>Whole kidney attenuation</td>
<td>Radionuclide renography</td>
<td>95 % LA (approx): -8–8 % points</td>
<td>Convenient routine protocol</td>
<td>Illogical parenchyma attenuation correction</td>
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<tr>
<td>Hackstein, 2007 [31]</td>
<td>4-detector MDCT</td>
<td>Extended 3-phase routine scanning</td>
<td>“Two-point Patlak plot”</td>
<td>⁹⁹ᵐTc-MAG3 renography</td>
<td>95 % LA: -11.2–10.2 % points</td>
<td>Available data efficiently used for dynamic study</td>
<td>Some additional radiation; interpolation required</td>
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Aims of the study

General aim
The general purpose of this work was to develop and evaluate a method for assessment of split renal function with computed tomography, primarily in the setting of the living renal donor investigation.

Specific aims
1. To investigate the feasibility of a modification of a previously described procedure for calculation of split renal function from CT, applied to a study material of renal donors. (I)

2. To further validate the described method in a patient material with higher prevalence of renal pathology expected to influence the split renal function. (II)

3. To evaluate a method for the same purpose facilitated by an advanced software tool for volumetry. (II)

4. To evaluate a scanning technique of the kidneys with MRI based on respiration triggering for a dynamic study of the renal function. (III)

5. To investigate the usefulness of a formula for approximation of renal volume and split renal function with CT. (IV)

6. To study the significance of choice of contrast phase with CT for the results of split renal function. (IV)
Material

Patients

Paper I was a retrospective study of subjects undergoing investigation for living renal donation from 1997 to 2001. Although 102 living donations were performed at our centre during the period, only 27 individuals could be included in the study group for comparison between CT and renography. Three causes of falling off were identified: (1) conventional DSA and IVP were performed instead of CT, (2) CT was performed at a different centre and the image material was not available, or (3) the CT image material was incomplete, e.g., the entire kidneys were not depicted, or a deviating protocol was used.

In paper II, ad hoc analysis of a prospective study of different diagnostic methods available for detecting clinically significant renal artery stenosis was made. Fifty-eight patients were studied between 2001 and 2004, and the comparison included CT angiography (CTA), MR angiography (MRA), duplex ultrasonography and captopril renography. Transstenotic pressure gradient measurement was used as reference method for hemodynamical significance [34]. Thirty-eight patients underwent both CTA and renography and were included in the study in paper II. The main reason for exclusion from either of the examinations was a serum creatinine equal to or above 200 μmol/L, which was defined to disqualify for CT examination.

Principally the same subjects as in paper II also constituted the study material in paper III. In a consecutive subset of 26 of the patients examined with MRA, a dynamic contrast-enhanced MR examination of the kidneys was accomplished during the same session. All of these patients also underwent renography, and 16 of them underwent CTA, the exclusion criteria being the same as in paper II. A comparison between MRI and renography was made in paper III, and between MRI and CTA where available. However, a comparison between CTA and renography was not presented, as partly the same data was previously published in paper II.

In paper IV, patients solely examined with CT of the urinary tract were studied. Clinical, consecutive CT examinations aimed at investigating macroscopic hematuria, in which no significant pathology was detected, were included. As not all patients had identical CT protocols, a total of 64 examinations were included to agree with the number needed for statistical power in the subgroups involved in the study.
**Methods**

**99mTc-MAG3 Renography**

The gamma camera used in the study was a Picker SX-300 Digital Dyna Camera (Picker International, Cleveland, USA) equipped with an LEGP parallel-hole collimator, matrix size 128 × 128 pixels. The patients were examined in supine position, with the back against the collimator. Simultaneously with a bolus injection of 80 MBq $^{99m}$Tc-MAG3, image acquisition started with 1 second per frame during the first 3 minutes and thereafter 10 seconds per frame for a total of 180 frames. In papers II and III, where the primary aim of the renography was detection of renal artery stenosis, captopril enhanced examinations were routinely performed. A baseline examination was first performed in those patients not on medication with an ACE inhibitor or angiotensin receptor blocker. After 2 – 3 hours, 25 mg captopril was given orally and blood pressure was monitored every 15 minutes. After one hour, the gamma camera examination was repeated, according to the description above.

Figure 4 demonstrates a normal renogram. The convention for projection of the images needs to be observed, with the right kidney to the right in the renogram frames. Regions of interest (ROI) were drawn manually around the kidneys and on the heart area, and automatically for the extrarenal areas. The time-activity curve generated from the heart ROI was used as plasma input curve. The processing was then made according to the Patlak-Rutland algorithm described above. From the plot, the slope for each kidney was calculated with a linear regression analysis and the results were calculated as each kidney’s fraction of the total in percent.
Figure 4.
A $^{99m}$Tc-MAG3 renogram of a 62-year old male patient with normal appearance and normal split renal function.
The use of different CT techniques for the different parts of this study reflects the technical development during the last decade. In the first paper, with patient material ranging from 1997 to 2001, a single detector CT scanner was used (Somatom Plus 4, Siemens, Forchheim, Germany), while in the subsequent papers, this had been upgraded to a 16-channel MDCT scanner (Somatom Sensation 16, Siemens, Forchheim, Germany). The hardware and software applications for image processing illustrate a similar evolution; from a MagicView workstation in paper I, to the Leonardo workstation (both Siemens, Forchheim, Germany) which was a key feature for the processing in papers II-IV. An analogous equipment was also evaluated in paper II, where an Impax PACS workstation (Agfa-Gevaert, Mortsel, Belgium) with an integrated volume rendering software, Voxar 3D (Barco, Kortrijk, Belgium), was used for volumetry.

The specific contrast media also differed between the papers. Iopromide 300 mg I/mL (Ultravist, Schering, Berlin, Germany), in doses ranging from 70 – 180 mL, was used for the contrast enhanced CT examinations in papers I to III. During the course of collection of data for paper IV, the local clinical routine was altered from using iohexol 300 mg I/mL (Omnipaque, GE Healthcare, Little Chalfont, England) in a dose of 80 mL to iobitridol 350 mg I/mL (Xenetix, Guerbet, Villepinte, France) in a dose of 70 mL. All agents are non-ionic tri-iodinated compounds with similar pharmacokinetic properties.

The overall principle applied to split renal function measurement from CT was adapted from a preceding study [26]. It was postulated that the total attenuation value of contrast medium in the kidney, $H_{U_{tot}}$, will represent the relative function of that kidney. This property can be characterized as the product of the kidney’s volume and mean contrast attenuation value in the parenchyma. The methods for acquisition of these two variables were subsequently modified in the papers. The principle in Paper I included manual placement of a ROI over the renal parenchyma in all $n$ axial sections of the respective kidney, each with a slice thickness $t$. From each ROI, the mean attenuation, $H_U$ and area $A$ was obtained. The volume $V$ of the kidney was calculated as the sum of all slice volumes,

$$V = A_1 \cdot t + A_2 \cdot t + \ldots + A_n \cdot t$$
according to the slice summation method, also applicable to MRI [35]. For the total attenuation of the kidney, $\text{HU}_{\text{tot}}$, the factor $\text{HU}$ of each section was included:

$$\text{HU}_{\text{tot}} = \text{HU}_1 \cdot A_1 \cdot t + \text{HU}_2 \cdot A_2 \cdot t + \ldots + \text{HU}_n \cdot A_n \cdot t$$

If this is rearranged to:

$$\text{HU}_{\text{tot}} = t \cdot (\text{HU}_1 \cdot A_1 + \text{HU}_2 \cdot A_2 + \ldots + \text{HU}_n \cdot A_n)$$

the implication is that slice thickness $t$ can be omitted for the calculation of split renal function, as it is constant to both kidneys. In Paper I, this principle was adjusted to the amount of data and instead of all slices, every six or nine slices was evaluated, depending on the increment used in the present material.

With the workstation used for Paper II (Leonardo, Siemens, Forchheim, Germany), free image reconstructions were possible. To condense the data quantity, 5 mm thick slices in an oblique coronal plane were reconstructed, thus taking the entire renal volume into account and improving the handling. An identical procedure was employed for the supplementary CT measurement in Paper III. An alternative method was also evaluated in Paper II, involving automatic VOI (volume of interest) definition and volume measurement. With the software used, Voxar 3D (Barco, Kortrijk, Belgium), a cohering volume could be automatically selected from a volume rendered three-dimensional reconstruction, provided that the contrast to the surroundings was sufficient. From a selected VOI, volume and mean attenuation was automatically obtained.
In Paper IV, an additional method was evaluated as an effort to further develop the volume measurement. For that purpose, a formula originally derived for ultrasonographical estimation of renal volumes [36] was transferred to CT. The formula was introduced as an alternative to the ellipsoid formula, which has generated inaccurate results of renal volume [35]. The new formula takes into account two variables (Figure 5) – maximum length of the kidney ($ML$) and maximum cross section area ($MCA$):

$$V = 0.353 \times ML^{1.8} \times MCA^{0.6}$$

Assessment of mean attenuation of each kidney was made from a single axial image including representative sections of each kidney, rather than from the entire kidneys. As reference for split renal function in Paper IV, a semi-automatic volumetric software application was used (“Volume” on a Leonardo workstation). With this tool, a VOI is defined through interpolation of a number of manually placed ROIs in the axial slices.

**Figure 5.**
The variables required for calculation of the renal volume based on the approximation formula.
MRI

For the dynamic MRI examination in paper III, a 1.5 T system was used (Gyroscan NT Intera, Philips Medical Systems, Best, the Netherlands) with gradient specifications: amplitude 30 mT/m, rise time 200 s, slew rate 150 mT/m/ms, and with a phased array body coil. An oblique coronal plane depicting a representative section of both kidneys was selected. The respiratory triggering mechanism was set to start the scan at end-expiration of each cycle. A two-dimensional RF-spoiled gradient echo sequence was used with TR 9.3 ms, TE 4.6 ms and flip angle 40°. After initiating the scanning, 2 mL of gadodiamide (Omniscan™, 0.5 mmol/mL Gd-DTPA-BMA (gadodiamide), GE Healthcare, Oslo, Norway) was administered as a bolus injection in an antecubital vein, manually as fast as possible. The imaging was synchronized with the respiration by means of the standard equipment for respiratory triggering included in the MRI system. Image acquisition was triggered at end-expiration in each breathing cycle. A total of 200 respiratory triggered images were obtained, and hence, the total examination time would depend on the respiratory frequency of the individual.

The principle of contrast enhancement with MRI differs from that applicable to X-ray techniques. In the latter cases, the contrast medium is directly visualized in the image, depending on its radiation attenuation. In MRI on the other hand, the effects exerted by the contrast agent on the surrounding tissues are reflected in the enhanced tissue differentiation, rather than the substance per se.

For this study, the paramagnetic metal gadolinium was used as contrast agent. To eliminate the toxicity of gadolinium, it is administered as a chelate with a ligand (in this case, DTPA-BMA). The gadolinium chelate is distributed in the extracellular volume and eliminated through glomerular filtration, and is therefore potentially useful as a filtration marker. The effect of gadolinium on signal intensity is a shortening of the T1 (and T2) relaxation time in its surrounding. This implies increased signal intensity of the currently affected tissue in a T1-weighted study. However, the physical conditions makes the relationship between tissue concentration of gadolinium and signal intensity considerably more complicated than the linear connection of iodine concentration and attenuation value in a CT image. A key problem has been to find a range of concentration within which linearity can be approximated, a question which has been investigated in prior studies [37-40]. The general principle is to use a strongly T1-weighted pulse sequence, and to keep the contrast dose low to minimize non-linearity effects from high gadolinium concentrations accumulating in the collecting systems.

The principle for timing of the image acquisition in Paper III – respiratory triggering – was presented as a means of overcoming a problem following from dynamic renal studies: the mobility of the kidneys. With renography, this is of
little concern due to the low resolution, but with MRI, imaging acquired without attention to respiratory related motion of the kidneys increases the risk of motion artefacts and leads to increased effort with the image processing. The common ways to deal with this have included imaging during breath-hold [38] or “shallow breathing” [40]. To make imaging for up to 20 minutes possible with preserved high temporal resolution, respiratory triggering was hypothesized to be advantageous.

An example of a signal-curve of a single kidney resulting from the dynamic MRI study is demonstrated in Figure 6. A constant breathing rate was assumed, and the x-axis was converted to a time scale based on the total examination time. For calculation of relative renal function, an integral method was employed. The first image where a rise in signal intensity in the kidneys was observed was set as starting point, and the integral of the curve from 1.5 to 2.5 minutes thereafter was computed. This value would represent relative renal function per volume unit. From axial T2-weighted images obtained during the same session as the dynamic scanning, the volume of the respective kidneys was calculated according to the principle of slice summation, or voxel count, method [35]. The renal function per volume unit was multiplied by the volume of the respective kidney to result in a value, in arbitrary units, for comparison and calculation of split renal function. The integral method has been assumed to be comparable to the Patlak-Rutland plot in scintigraphic studies [41], and has been evaluated in MRI applications [38, 40], with favourable results.

![Signal curve of a dynamic contrast-enhanced MRI study from Paper III.](image_url)
**Statistical methods**

The recurrent question in this study was to compare the results of two methods measuring the same property where no gold standard measurement was available for reference. In this matter, no statistical test can discriminate whether the agreement between the two methods subject to comparison is ‘good enough’. Rather, it is a question of clinical judgment to define which measurement difference is acceptable in the specific context. A frequently used principle has been to perform a linear regression analysis of the two variables. The correlation coefficient, with associated p-value, is then interpreted as the agreement between the two methods. Bland and Altman discussed the rationale behind this and pointed out the potential risks and theoretical disadvantages of this approach [42]. As an alternative, a new model for descriptive statistics was proposed, which has become the most commonly used model for presenting and discussing method agreement, known as the Bland-Altman method [42]. Assuming normal distribution of the variables, the Bland-Altman plot graphically describes the distribution of differences throughout the scale of measurement results and defines the limits within which 95% of the measurement differences are predicted to occur, i.e., a confidence interval. These boundaries are commonly denoted the “95% limits of agreement”. In other words, the model answers the question: “Given a result obtained with method A, what maximum difference from a result in the same individual can be expected with method B in 95% of the cases?”

The Bland-Altman algorithm was used as the main descriptive model throughout this study, from paper II onwards. In the following results section, the data from paper I are also presented with this model. Although not recommended by the originators of the Bland-Altman method, papers I to III also give the correlation coefficients for the respective method comparisons, mainly because of the general recognition of that principle for data presentation.

**Principle for report of results**

The presentation of data in this study has some common, basic features. The principal aim has been to measure and evaluate relative renal function as an internal comparison of the two kidneys of an individual, rather than to present absolute measurements of renal function. The values of individual renal function on which the split renal function is based are given in arbitrary units and are not of interest per se. Hence, the key unit in this study is percent, which has some certain implications. A complete presentation of results would include a pair of percentages in each individual, e.g., right kidney 65% and left kidney 35%. For simplicity, however, only the percentage of the right kidney is presented. It is therefore important not to misconceive a statement that the right kidney represents 65% to mean 65% of that kidney’s “original” function, assuming previous symmetrical conditions.
One additional convention regarding the presentation of results needs observation. With a study of relative differences of entities measured in percent, the risk of confusion is apparent. Figure 7 schematically illustrates a pair of kidneys, with split renal function estimated with two different methods. The heights of the bars represent their individual function according to the respective method, in an arbitrary unit. Below are stated some of the variables possible to use for the description of the difference between the kidneys, and between the methods. Hence, the risk of mixing up the concepts is clearly noticeable. The numbers in bold style indicate which principle is employed in this study. Thus, in an attempt to preserve clarity, split renal function is presented as the right kidney’s share in percent, whereas differences in split renal function between methods are presented in percentage points. This is a generally used standard for presentation of similar data.

Results are routinely presented as mean ± standard deviation, with the 95% limits of agreement according to Bland-Altman analysis within parentheses, unless otherwise stated. It should be noted that in Paper II, the results were presented with the absolute values of the observed differences, rather than the true differences with a positive or negative sign. In the following section, those results were recalculated to harmonize with the results of the other papers.
**Figure 7.**

Arbitrary results of split renal function according to two different methods, with examples of possible variables to describe differences. The numbers in bold style indicates which measures have been used in this study. SRF, split renal function.

<table>
<thead>
<tr>
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<th>Method A</th>
<th>Method B</th>
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<td>53.3</td>
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<tr>
<td>Split renal function (%)</td>
<td>52.6</td>
<td>44.4</td>
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<tr>
<td>Clearance (a.u.)</td>
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<td>-6.3</td>
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<tr>
<td>Side difference, clearance (a.u.)</td>
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<td>13.3</td>
</tr>
<tr>
<td>Side difference, SRF (% points)</td>
<td>-5.3</td>
<td>11.1</td>
</tr>
<tr>
<td>Side difference, SRF (%)</td>
<td>-11.1</td>
<td>25.0</td>
</tr>
<tr>
<td>Method difference, clearance (a.u.)</td>
<td>9.8</td>
<td>-9.8</td>
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<tr>
<td>Method difference, SRF (% points)</td>
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<td>8.2</td>
</tr>
<tr>
<td>Method difference, SRF (%)</td>
<td>-17.3</td>
<td>-18.4</td>
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Results

Paper I

In this study, $^{99m}$Tc-MAG3 renography and CT were compared in 27 previous potential donors. CT was performed with a single-detector spiral CT scanner and the examinations were made in corticomedullary and excretory phases, aimed at mapping arterial supply and outflow system. The total contrast attenuation of the kidneys was calculated in each of the contrast phases and compared with the results of split renal function from renography.

The mean difference of renography and corticomedullary phase CT was $-3.6 \pm 3.6$ (-10.7–3.4) percentage points. A Bland-Altman plot of the differences is shown in Figure 8. For renography and excretory phase CT, the mean difference was $-2.1 \pm 2.8$ (-7.5–3.3) percentage points. Figure 9 displays the corresponding Bland-Altman plot.

![Bland-Altman plot](image)

Figure 8.
Bland-Altman plot of the comparison of renography and corticomedullary phase CT in paper I (n = 27). The coordinates (49; -2), (49; 1) and (52; -4) contain overlapping data points. The mean difference between the methods was -3.6 percentage points (solid horizontal line), with 95% limits of agreement of -10.7 and 3.4 percentage points (dashed horizontal lines).
The ratio between renal volumes in a subject was found to be a strong predictor of the function ratio, according to the measurements from CT. A difference in craniocaudal difference between the two kidneys was also noted to explain the bias in the results with the corticomedullary phase CT. As the right kidney normally is located more caudally than the left one, the right kidney will be scanned at a later time-point, on an average. With a single-detector scanner, this time difference will be large enough to make the continuing contrast material uptake significant. Thus, the caudal kidney will be overestimated according to this measurement. The bias is demonstrated in Figure 8 by the displacement of data points from the zero line. A similar tendency, although weaker, was observed in the excretory phase. However, the explanation was less obvious in that scenario, as the effect described for corticomedullary phase could not be considered to have any significance several minutes after injection of contrast agent.

Figure 9.
Bland-Altman plot of the comparison of renography and excretory phase CT in paper I (n = 27). In the graph, overlapping data points exist with the coordinates (49; -3), (49; -2) (3 points), (49; -1), (49; 2) and (51; -1). The mean difference was -2.1 percentage points (solid horizontal line), and 95% limits of agreement were -7.5 and 3.3 percentage points (dashed horizontal lines).
Papers II and III

A similar method comparison was conducted in Paper II, and then further extended in Paper III. Both studies constituted ad hoc analyses of a prospective comparison of diagnostic methods for renal artery stenosis. In paper II, a study analogous to the comparison in paper I was made including $^{99m}$Tc-MAG3 renography and corticomedullary phase CT. Thirty-eight patients with suspected renal artery stenosis were studied and the mean difference was 0.1 ± 5.9 (-11.4–11.6) percentage points, graphically illustrated in Figures 10 and 11. Hence, the bias observed in Paper I was not reproduced, and this was interpreted to depend on the faster multidetector scanner used in this study.

![Bland-Altman plot](image)

**Figure 10.**
Bland-Altman plot of the comparison of renography and CT in paper II (n = 38). The mean difference was 0.1 percentage points (solid horizontal line), and the 95% limits of agreement -11.4 and 11.6 percentage points (dashed horizontal lines).
Figure 11.
Scatterplot of the comparison of renography and CT in Paper II (n = 38). The dashed line represents the line of equality.
A comparison of two different methods to assess the total contrast attenuation value from CT was made. A method for automatic volumetry was studied, with the traditional method, requiring manual ROI placement in the individual CT sections, as a reference. The mean difference in split renal function with that evaluation was $0.4 \pm 1.4$ (-2.3–3.1) percentage points, thus expressing close agreement. However, the results can be subdivided into separate investigation of the volumes obtained with the respective method. Such analysis indicates a range of differences from underestimation by 58 cm$^3$ to overestimation by 42 cm$^3$ with the automatic method, and an average difference of 7 ± 21 cm$^3$ (mean ± standard deviation). Figure 12 displays the volume comparison graphically, with right and left kidneys separated.

**Figure 12.**
Renal volumes measured by manual and automatic methods in Paper II (n = 76).
In paper III, dynamic contrast-enhanced MRI of the kidneys was evaluated for the purpose of split renal function calculation in 26 patients. To counteract the motion of the kidneys which renders the processing of dynamic examinations difficult, a principle of respiratory triggered imaging was investigated. Apart from one MRI examination which had to be discarded because of fold-over artefacts, the respiratory triggering generated high quality dynamic studies with average duration of 14 minutes (range 8–20). Motion artefacts obliged exclusion of 0.1% of the total image material and with those pictures excluded, highly reproducible ROI positioning was generated. The difference between MRI and renography in 25 subjects was -1.6 ± 6.6 (-14.6–11.4) percentage points, and the data is presented in Figures 13 and 14.

Figure 13.
Scatterplot of the comparison of renography and MRI in Paper III (n = 25). The dashed line represents the line of equality.
Figure 14.
Bland-Altman plot of the data in Figure 13.
The difference between CT and MRI could be evaluated in 15 of the 25 patients, and amounted to \(-1.7 \pm 5.7\) (-13.0–9.5) percentage points.

Combining the data from Papers II and III, all three techniques to obtain a value of split renal function were utilized in 15 patients, illustrated in Figure 15. The deviation from a mean value of the other two methods was similar with the three modalities: renography differed on average 0.1 ± 4.3 percentage points, MRI 1.2 ± 4.7 percentage points and CT -1.4 ± 4.9 percentage points (mean ± standard deviation). ANOVA testing did not detect any significant difference in mean value between the groups (p = 0.94).

![Figure 15](image-url)

**Figure 15.**
The results of split renal function by renography, MRI and CT (n = 15).
This study was conducted to further investigate the possibility of simplifying the investigation procedure, but from the perspective of the physician. The traditionally used algorithm with CT includes manual ROI placement in each individual CT slice and collection of the values of area and mean HU number. This is a time-consuming and monotonous procedure with manual handling of large amounts of data, implying a risk of errors. Reconstructing the image material with thicker slices reduces the quantity of data, but at the expense of spatial resolution and with increased partial volume effects. Automatic volumetric methods, as evaluated in Paper II, are promising but still have limited availability and flexibility. A semi-automatic volumetric tool has been reported to be useful [28], but did in our experience not considerably facilitate the manual work.

A formula originally derived for ultrasonographical renal volume measurement was evaluated in 64 patients examined with CT of the urinary tract. The mean difference in split renal function from the reference results obtained by means of the above-mentioned semi-automatic volumetric tool was -0.7 ± 1.6 (-3.9–2.4) percentage points, i.e., a minor bias and a range of differences slightly exceeding the 3 percentage point limit defined as relevant. The volumes of all individual kidneys with the two methods are presented graphically in Figure 16, and in the Discussion section, in Figure 22.

The second aim of Paper IV was to evaluate the influence of contrast phase selection for the calculations from CT. In 43 patients, both corticomedullary and nephrographic phase were included in the examination, and the mean difference in that comparison was 0.3 ± 0.9 (-1.4–2.0) percentage points.
Figure 16.
Kidney volumes obtained with a semi-automatic volumetric software tool, and with a manual method based on an approximation formula (n = 128). Mean overestimation by the manual method was 12 ± 14 (-15–39) cm³.
Discussion

The great potential of generating functional information of the kidneys from contrast-enhanced CT is essentially uncontroversial. The different properties that sum up to yield the exceptional prerequisites for this are well understood:

1. A filtration marker is present, i.e. the iodinated contrast agent.
2. The concentration of the filtration marker is proportional to a value which is easily measured, i.e. the HU number in the CT image.
3. The high spatial resolution allows for easy demarcation of the regions of interest and exclusion of irrelevant structures.

Likewise, the aspects that discourage from the exploitation of this potential are easily pointed out:

1. The examination is associated with radiation exposure.
2. The contrast agent is potentially harmful to the kidneys.

These advantages and disadvantages are weighed differently depending on the specific setting. In a patient with renal disease that necessitates the investigation of split renal function, it is likely that avoiding contrast induced nephropathy is of great importance and that the radiation exposure has less influence on the choice of imaging modality. On the other hand, when a potential renal donor has passed the first steps of scrutiny and is qualified for the imaging part, their renal function is known not to be impaired, and contrast induced nephropathy will be of relatively little concern. More worry should, in that scenario, be addressed to the radiation aspect of the examination. That was also one of the key conditions of this study: to design the protocol in order to maintain diagnostic accuracy while minimizing nuisance and risk for the individual.
In the previous reports of methods for determining relative renal function from CT, the main focus and priority has varied between these two principal situations mentioned above. A nearly parallel distinction can be made concerning the means to derive a new technique: from attempts to produce theoretically attractive physiological models on one hand, to more pragmatic approaches on the other hand. The method proposed by Dawson and Peters [24] has theoretical benefits regarding its way of reflecting renal uptake and excretion. Only later, it was shown to agree well with the standard method [25]. However, the nature of such procedures makes them unrealistic in the donor context, as previously discussed. Conversely, the model of Frennby et al [26, 27] and its followers [28, 29], had the practical usefulness as basic prerequisite, and validation against the current method of choice was the primary objective. The model of Hackstein et al [30-33, 43] was based on a careful theoretical derivation which was fit into a standard protocol for contrast-enhanced CT by means of some assumptions and simplifications. Validation against a method for assessment of split renal function also took long and did not seem to have been regarded as a main point. From the results displayed in Table 1, it appears that the gamma camera agreement was slightly better with the “Frennby model” [28] than with the “Hackstein model” [31]. It might also be worth noting that one of the authors of the original article [24] participated as a co-author recommending the modernized Frennby model [28].
In the explorative study in Paper I, the aim was to evaluate a modified version of the principle of measuring whole kidney attenuation at one time-point [26]. At our institution, nephrographic phase has not been considered indispensable for detecting renal parenchymal pathology, and to minimize the radiation dose, the examinations at hand therefore included unenhanced, corticomedullary and excretory phase scans. In the corticomedullary phase images the boundaries separating cortex and medulla are clearly visible, reflecting the great difference in blood flow to the respective tissue type (Figure 17). In this phase, the majority of the contrast material is located in the vascular compartment, and filtration has only occurred to a minor extent.

Figure 17.
Contrast-enhanced CT scanning of the kidneys in corticomedullary phase. A ROI has been drawn around the left kidney.

The motivation for attempting to estimate split renal function from the corticomedullary phase came from the principles for regulation of blood flow and glomerular filtration in the kidneys. In the Introduction section, it was stated that the kidneys receive 20% of the cardiac output to be able to produce the large quantities of primary urine required for water and solute balance regulation. Since the systemic arterial blood pressure varies considerably over the day depending on degree of activity and sympathetic tone, the kidneys might be suspected to be directly affected by those changes. However, the kidneys possess sophisticated intrinsic mechanisms for auto regulation of their blood flow, keeping it virtually constant within the ranges of normal blood pressure, from approximately 70 to 180 mmHg.
Mechanisms for renal autoregulation

Two different mechanisms account for this regulation. Firstly, the myogenic feedback mechanism involves the smooth muscle cells of the afferent and efferent arterioles of the glomerulus. Stretching of the muscle cells caused by increased tension in the vessel wall makes the arteries and afferent arterioles respond with contraction and thus keeping the renal blood flow constant. The second instrument for autoregulation is known as the tubuloglomerular feedback mechanism. This involves certain cell populations in the nephron known as macula densa, located in the distal tubule, where it passes closely to its own glomerulus. The macula densa cells contribute to a larger system called the juxtaglomerular apparatus, further consisting of specialized cells of the vessel walls of the afferent and efferent arterioles. The tubuloglomerular feedback is a response to alterations in the tubular fluid flow, increasing the secretion of vasoconstrictive substances, e.g., renin, thus activating the RAAS (Figure 3).

The glomerular filtration rate ($GFR$) is depending on the net filtration pressure ($NFP$) in the glomerulus and the so-called filtration coefficient ($K_F$), which comprises the glomerular capillary area and the hydraulic permeability of the capillaries:

$$GFR = K_F \cdot NFP$$

The net filtration pressure is the sum of the hydrostatic pressures over the glomerular membrane, i.e., Bowman’s capsule hydraulic pressure ($P_{BC}$) and colloid osmotic pressure in the glomerular capillary ($\pi_{GC}$) subtracted from the glomerular capillary hydraulic pressure ($P_{GC}$) (Figure 18).

![Figure 18.](image_url)

A schematic glomerulus. ($NFP = P_{GC} - P_{BC} - \pi_{GC}$). The colloid osmotic pressure in Bowman’s capsule ($\pi_{BC}$) can normally be neglected, as its protein content is low.
The hydraulic pressure in the glomerular capillary is closely connected to the renal arterial blood pressure, but may also be separately regulated by changes in the resistance of the afferent and efferent arterioles, respectively. Under normal conditions, the GFR is regulated parallel to the renal blood flow to be maintained at a constant level independently on daily variations in systemic arterial pressure. Hence, we hypothesized that although the corticomedullary phase of the CT scan mostly reflects the perfusion of the kidneys, this may serve as an indirect measure of the GFR.

The results in Paper I were somewhat discouraging, as displayed in Figure 8. A clear bias was observed in the comparison of corticomedullary phase CT with ⁹⁹mTc-MAG3 renography, implying overestimation of the right kidney by CT. A straightforward explanation for this was found, previously described in the Results section, as the relatively long scanning time led to considerably increasing contrast attenuation values in the caudal poles scanned the latest.

As for the investigation of excretory phase scanning in Paper I, the results were slightly better, at least partly depending on the absence of systematic error described with corticomedullary phase. However, it is theoretically even more difficult to justify the sole use of excretory phase for split renal function estimation. As a substantial proportion of the contrast material has left the kidneys at that time-point, a lower attenuation value in the parenchyma could depend on either a lower uptake of the contrast medium in the earlier phase, or a faster excretion. The latter scenario would then lead to an incorrect conclusion. A model including both contrast phases, similar to the one proposed by Hackstein [31], could have been considered, but in view of the intrinsic error associated with the corticomedullary phase, that option was discarded.
Paper II

Apart from the bias in Paper I, the results were essentially inconclusive due to the narrow distribution of results. It was hence assumed that by improving two aspects of the materials and methods, more decisive results could be acquired: faster scanning and a wider spectrum of results. To match those requirements, the study in Paper II was conducted, with both conditions fulfilled. Firstly, a 16-channel MDCT was used, considerably lowering the scanning time and reducing the problem associated with that. Secondly, the target group for the study was patients undergoing investigation for suspected renal artery stenosis, which suggested a certain prevalence of uni- or bilateral renovascular pathology with implications for the split renal function.

Limitations

However, some drawbacks were directly noticed in that study as well. The CT examinations, which were primarily conducted for CTA purposes in Paper II, did not include unenhanced scans. As a result, the attenuation value of pure parenchyma was not available for background correction, as instructed in the original description [26]. In Paper I, parenchyma correction was observed not to influence the results, but in cases of greater side differences, such adjustment was expected to be important. The second potential weakness concerned the gamma camera renography procedure. Intending to detect potentially curable renovascular hypertension, those examinations were in the present context performed with captopril enhancement. Captopril, an ACE inhibitor, affects mechanisms fundamental to the present discussion. In a kidney with hemodynamically significant renal artery stenosis, a pressure gradient over the stenosis is present, causing a lower arterial blood pressure distal to the stenosis. The kidney responds to this in the same way as if the systemic blood pressure was lowered, i.e., by initiating the RAAS mechanism aimed at raising the pressure (Figure 3). One of the local effects of angiotensin II is a selective vasoconstriction of the efferent arterioles, with the consequence of maintaining the glomerular capillary hydraulic pressure, and hence GFR, despite the lowered blood pressure. Hence, the net effect is a divergence between GFR and renal blood flow. The mechanism of an ACE inhibitor is to block the conversion of angiotensin I into the active form angiotensin II, and consequently to lower the angiotensin-dependent glomerular pressure upholding the filtration rate. With a glomerular filtration marker, the influence of an ACE inhibitor is a lowered uptake in an affected kidney. However, with $^{99m}$Tc-MAG3, which is excreted by tubular secretion, the principal effect is retention of tracer due to the decreased urine flow and delayed washout from the tubules (Figure 19).
Figure 19.
A captopril enhanced $^{99m}$Tc-MAG3 renography of a 59-year old female patient with suspected renal artery stenosis. The retention of tracer in the right kidney, as indicated in the frames to the right and in the curve below left, led to high suspicion of right-sided renovascular hypertension according to the review of the examination. Interestingly, pressure gradient measurement indicated pronounced, equal pressure gradients of 160 mmHg bilaterally.
Since one of the major indications for investigation of renal artery stenosis is a therapy-resistant hypertension caused by the high level of RAAS activation, a majority of such patients is likely to be on medication with an ACE inhibitor (or an angiotensin receptor antagonist) prior to a captopril renography examination. That was also the case in the present material, where 32 out of 38 individuals were prescribed such therapy. Despite recommendations [44], the ACE inhibitor administration was not suspended ahead of the study, which has been reported to decrease the sensitivity of the examination [45]. In the six patients not subject to chronic ACE inhibitor administration, the renography was initially performed as a baseline study. For the CT examinations in the same subjects, no instructions or alterations concerning the pharmacological therapy were made, implying that chronic ACE inhibitor therapy was maintained as usual during the study. According to the discussion above, such therapy would tend to diminish the divergence between renal blood flow and GFR seen in subjects with high RAAS activity and consequently, lead to increased accuracy of measurements in corticomedullary phase. In the six “ACE inhibitor naïve” subjects, the baseline renography study was used for comparison with CT to match the conditions. Following from the previous arguments, greater discrepancy might be expected between CT and renography in case of renovascular hypertension, but with the small patient number at hand, such conclusions could not be drawn. The prevalence of significant renal artery stenosis was not presented in Paper II, as that was not considered relevant for the present discussion. The original study gave those results in detail [34].

**Background correction**

From the plot in Figure 11, it appears as if extreme values were less extreme with CT than with renography. This was explained, as previously discussed, by the absence of parenchyma correction, likely to underestimate side differences. Similar results of method comparisons with a slope of the regression equation < 1.0 have in other instances been described as an expected outcome explained by a well-known statistical phenomenon called regression towards the mean [46]. However, when studying examples from the present data, it becomes clear that the agreement would be improved by such correction: The two most extreme values in the respective ends of Figure 11 represent split renal function of 3% and 92% by renography, and 15% and 84% by CT. In a different, consecutive CT material, mean renal parenchyma attenuation was measured to 35 HU. Correcting the attenuation values underlying the CT calculations by that value would alter split renal function in the examples from 15% to 8% and from 84% to 91%, respectively. It is inferred that parenchyma correction is necessary for maximum accuracy, particularly in cases of substantial side difference. In the absence of unenhanced parenchyma values to use for background correction, a different
suggestion has been to subtract by a HU value obtained from the psoas muscle of the study subject [28]. This appears more arbitrary than to use a standardized number as in the example above, and cannot be recommended.

Renography errors

One additional example in the present material highlights the subjectivity sometimes encountered in the interpretation of gamma camera renography studies. In one specific individual, split renal function according to CT was 59%. In the analysis of the corresponding gamma camera examination, it was stated that a low bilateral signal level made the assessment difficult. Although the Patlak-Rutland plot gave a result of 57%, the physician decided to assign the kidneys 50% each due to the uncertainty. Hence, what may seem like absolute facts is occasionally the result of a personal judgement possibly not intended for far-reaching conclusions.

In a consensus report of gamma camera renography [41], it was emphasized that few data were available concerning the accuracy and reproducibility of the method. Development of phantom models was recommended for future validation, and such models have been recently presented [47], but not yet widely used for assessment of accuracy. Reproducibility has been quantified by means of ten gamma camera renography studies evaluated by 180 investigators [48]. Regarding the estimation of split renal function, the results in all ten studies were essentially normally distributed, with an average range of results of approximately 14 percentage points. The authors pointed out that the survey did not comment on the accuracy of the method, and that such claims would be difficult or impossible to accomplish. It is important to recognize that, although the routine method, gamma camera renography has not reached a status as gold standard for the present purpose [41, 49]. The gold standard method would include selective urine collection from ureteral catheters. However, not even then a true value would be ensured, unless the catheters were constructed to completely occlude the ureters.
Paper III

Thus, in an attempt to further illuminate the internal relationship between gamma camera renography and CT for the purpose of split renal function assessment, the study in Paper III was undertaken. In the absence of a readily available gold standard, the rationale was to introduce a third modality for unbiased comparison. This third modality – MRI – has theoretical advantages combining several of the benefits of both CT and gamma camera renography. The properties of contrast-enhanced MRI have led to recognition that assessment of relative renal function may be potentially feasible with this technique as well [37-40, 50]. Since MRI does not have the drawback of ionizing radiation exposure, the possibility of performing dynamic examinations is greater than with CT. That advantage is combined with a spatial resolution of MRI close to that of CT, although for donor purposes, the use of MRI is limited by an inferior detection rate of accessory vessels [51-53] and renal calculi. It is also known that the previous conviction of a minimal toxicity of the MRI contrast media in regular doses has needed revision. After the reports of the possible causative relationship of gadolinium chelates and the serious late adverse reaction nephrogenic systemic fibrosis (NSF) [54-56], the caution in administering gadolinium-based contrast material to individuals with impaired renal function is now essentially the same as for iodinated contrast media in CT [57]. For living kidney donors with normal renal function, this drawback is of little concern.

Despite these reservations, investigation of a dynamic contrast-enhanced MRI protocol for estimation of split renal function was considered valuable to the present discourse. The aims were to demonstrate the robustness of the respiratory triggering principle, which to our knowledge had not been previously described in a similar context, and to make a crosswise analysis of all three methods in the same study subjects, helpful to the overall interpretation. Respiratory triggering is a practical method not requiring supplementary equipment or software for its accomplishment. In Paper III, it was demonstrated to generate high quality studies with minimal motion artefacts. Furthermore, the method can be expected to increase the subjective tolerability to an MRI examination extending for up to 20 minutes in comparison to a procedure demanding shallow breathing or repeated breath-holds, and it produces higher temporal resolution than previous, alternative models [38, 40].

MRI pulse sequence settings

To ensure compatibility with a range of respiratory frequencies, a compromise was necessary in the selection of settings – mainly concerning the number of PE steps and averages – to give the fast acquisition time required. Parameters chosen to give strong T1 weighting included a short TE and a flip angle of 40°, which has been recommended as the lowest value for potentiation of the T1-shortening
effect of gadolinium and reduction of sensitivity to T₂* effects [40]. As previously demonstrated, low doses of gadolinium contrast agent are also preferable to obtain in vivo concentrations low enough to consider T₂* effects insignificant, and hence, to maintain the nearly linear relationship between signal and concentration for all aspects of the study [39]. However, in the present studies of renal uptake and excretion, the two points where gadolinium concentration were at risk of exceeding those limits of linearity were in the perfusion phase or the excretory phase, when the contrast material was concentrated in the papillae and excreted in the calyces, respectively. None of these points were included in the present model for estimation of the relative function. It is therefore also implied that the analysis in Paper IV does not make use of the full potential of the signal-time curve obtained in the dynamic MRI examination to study e.g. obstructed urinary flow.

Examples of high discrepancy

The results of the study of MRI in Paper III resemble those in Paper II of CT: while the ability of both methods to detect major side differences was similar to ⁹⁹mTc-MAG3 renography, in the ranges of normal function distribution, some scattering was present. In Figure 14, the individual study whose result differed the most between the two methods was located outside the 95% limits of agreement, with a split renal function of 55% and 40% as stated by renography and MRI, respectively. In analogy to a previous example of disagreement between CT and renography, this illustrates the uncertainty following from the limitations of renography. According to the MRI signal-time curve, the uptake and excretion of gadolinium chelate was bilaterally poor but nearly equilateral. The curves, displayed in Figure 20, have similar shapes and relative heights from the baseline level. The difference in level of the baseline is explained by field inhomogeneities, which is compensated by the baseline correction. However, substantially different renal volumes were obtained from the axial MR images; 153 and 200 cm³, respectively. Hence, the left kidney was assigned a relatively higher proportion of the total renal function, i.e. 60%. In Figure 21 the corresponding renogram is displayed. The appearance of the signal curves clearly demonstrates the difficulty in obtaining a reliable curve for the calculation. This is also reflected in the results: the original estimate used in Paper III stated 55% split renal function of the right kidney, whereas in the present, blindly recalculated renogram, this was altered to 45%.

An instance with a nearly opposite problem was observed, where the divergence of MRI from renography was more difficult to explain. A 62-year old male underwent gamma camera renography six weeks after MRI. The renogram, which was presented in Figure 4, showed equilateral and adequate uptake and excretion of ⁹⁹mTc-MAG3, with essentially normal split renal function. With
MRI, a visual overview of the uptake and excretion gave no indication of side difference. However, the signal curve of the right kidney had a notably higher relative signal rise from baseline, which resulted in split renal function of 60%. Such differences could be explained by a less evident sensitivity to ROI placement also present in the MRI context.

Although applied in a smaller study material, the comparison including all three methods gives some additional contribution to the overall analysis. It is evident that for a given subject, the distribution of the three modalities may result in any of the conceivable combinations; very close agreement of either none, two or three techniques (Figure 15). No noticeable systematic deviation of any of them was observed. The features common to the respective methods vary in a similar manner. Thus, CT and MRI both measure glomerular filtration and take the exact renal volume into account, MRI and renography both give dynamic uptake curves, and renography and CT both use markers quantified with uncomplicated linear relationships. Each method has known weaknesses, which in some instances readily explains the differences. Hence, none of them probably is perfect for the current purpose.

![Signal-time curve from a dynamic contrast-enhanced MRI examination of a 37-year old male patient with relatively poorly functioning kidneys bilaterally.](image)

**Figure 20.**
Signal-time curve from a dynamic contrast-enhanced MRI examination of a 37-year old male patient with relatively poorly functioning kidneys bilaterally.
Figure 21.
Renogram of the same patient as in Figure 20. Poor uptake bilaterally makes the definition of ROI difficult.
Paper IV

Methods for CT volume assessment

A prerequisite for the introduction of a method to obtain renal functional data from CT is a procedure that can be implemented as routine practice. As apparent from the previous descriptions, the information from CT, and specifically the volume information, can be acquired in a variety of ways. The manual algorithm presented in Paper I has the status of a reference method, as it gives detailed control of the exclusion of irrelevant structures. With properly set limits of the ROI, perirenal or hilar fat is automatically left out from the summation. A lower limit of 20 HU has been applied throughout this work, whereas an upper limit is less valuable but may possibly be set to ensure exclusion of e.g. renal calculi. A risk of human error is introduced as the method requires manual transfer of data to a separate spreadsheet for the calculation. By creating reconstructions of somewhat higher slice thickness and in a plane covering more parenchyma per slice, as in Paper II, the manual procedure is facilitated, but at the expense of detail resolution.

The method here referred to as “semi-automatic” is, by means of dedicated software, the natural extension to the manual algorithm. ROIs are manually drawn around the relevant structures in axial images, as with the original method. However, by defining ROIs in an arbitrary slice interval, the computer assists with interpolation of the intermediate slices. The interpolation process is monitored in the coronal and sagittal projections in real-time, thus serving as a direct assessment of the exactness. In a homogeneous structure with smooth borders this method is highly efficient. However, at the level of the renal hilum, the procedure is complicated by the irregular border and the vessels entering and leaving the kidney. Hence, ROI placement is necessary in virtually every slice to give accurate delineation. In a study with thin slices, the process is further hampered by the computer processing time required. However, when properly performed, this method is also considered a reference method, similar to the manual method.

The automatic method evaluated in Paper II takes the computer assistance one step further. In a rendered volume, continuous structures are directly selected and isolated. For this to be useful in the present context, some perirenal fat separating the kidneys from muscles, liver, spleen etc, is desirable. Although in such instances very fast, the method had vital deficiencies in manual adjustment possibilities. This was reflected in the results of the estimated volumes presented in Figure 12, indicating significant spread.
Table 2 summarizes the methods reviewed, including the new method introduced as a possible alternative in Paper IV. That model was proposed as an attempt to balance the demands for improving the management of the large image material with the need for preserved accuracy. Although the variables for the volume approximation formula are well defined, a risk of measurement error is present, as well as a risk of significant method error. Despite that, the results in Paper IV indicated a relative robustness of the method. Clearly, the method proved higher conformity with the reference method than the automatic volumetry tool did in Paper II. As indicated in Figure 22, the error obtained from the renal volume approximation method expressed as percentage was essentially constant over the range of volumes studied. On average, the formula overestimated renal volume by 7.1%. For the measures of split renal function, the approximation formula in most instances agreed well with the reference method, suggesting interchangeability. The defined acceptance limit of 3 percentage points was exceeded in isolated cases, one of which was explained by a presumed chronic obstruction.

Table 2.
Overview of different methods evaluated for estimation of renal volume.

<table>
<thead>
<tr>
<th>Principle</th>
<th>(Example of) equipment</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manual ROI placement (Paper I)</td>
<td>Any viewing software</td>
<td>Exact method, independent of advanced hard- or software</td>
<td>Time-consuming, requires manual handling of large data amounts</td>
</tr>
<tr>
<td>Automatic VOI definition (Paper II)</td>
<td>Voxar 3D</td>
<td>Fast method in selected cases</td>
<td>Limited accuracy and ability to make manual adjustments</td>
</tr>
<tr>
<td>“Semi-automatic” VOI definition (Paper IV)</td>
<td>“Volume” application of Leonardo workstation</td>
<td>Exact method</td>
<td>Relatively computer-dependent</td>
</tr>
<tr>
<td>Approximation formula (Paper IV)</td>
<td>“MPR” application of Leonardo workstation</td>
<td>Fast method, independent of advanced hard- or software</td>
<td>Inbuilt method error</td>
</tr>
</tbody>
</table>
Of significant value to the overall discussion was the answer to the secondary aim of Paper IV. The only previous studies of split renal function assessed from corticomedullary phase CT (Papers I and II) left some doubt concerning the true values of split renal function in ranges of normal and near-normal distribution. As other comparisons reporting close agreement of CT with gamma camera renography were applied to nephrographic phase [26, 28], it was considered relevant to perform an internal comparison of the two contrast phases. The results spoke in favour of the use of corticomedullary phase, as the agreement was close. One isolated instance of high differences was interpreted to depend on error associated with the acquisition of variables for the approximation method. It was observed that attenuation measurement could be restricted to a single axial slice; however, in the case of corticomedullary phase, specific carefulness is required to find representative slices for the measurement. This is attributed to varying distribution of renal columns in the separate slices.

**Figure 22.**
The difference in renal volume by the reference and approximation method expressed as percentage, correlated to the renal volume. The average error was -7.1 ± 7.7% (mean ± SD) (solid horizontal line). The 95% limits of agreement denoted by dashed horizontal lines were -22 and 7.9%.

**Contrast phase significance**
Of significant value to the overall discussion was the answer to the secondary aim of Paper IV. The only previous studies of split renal function assessed from corticomedullary phase CT (Papers I and II) left some doubt concerning the true values of split renal function in ranges of normal and near-normal distribution. As other comparisons reporting close agreement of CT with gamma camera renography were applied to nephrographic phase [26, 28], it was considered relevant to perform an internal comparison of the two contrast phases. The results spoke in favour of the use of corticomedullary phase, as the agreement was close. One isolated instance of high differences was interpreted to depend on error associated with the acquisition of variables for the approximation method. It was observed that attenuation measurement could be restricted to a single axial slice; however, in the case of corticomedullary phase, specific carefulness is required to find representative slices for the measurement. This is attributed to varying distribution of renal columns in the separate slices.
Conclusions

1. The estimate of split renal function based on whole kidney attenuation with CT is potentially useful; however, in corticomedullary phase the result is sensitive to the time required for scanning and therefore a single detector CT scanner is not recommended.

2. The detection of major side differences in split renal function with a 16-channel MDCT in corticomedullary contrast phase is comparable to 99mTc-MAG3 renography.

3. A volumetric software application is feasible for split renal function calculation with contrast-enhanced CT, giving results equivalent to a manual calculation method.

4. Respiratory triggering is useful for dynamic contrast-enhanced MRI of the kidneys with high temporal resolution, and a measure of split renal function equivalent to 99mTc-MAG3 renography and CT is obtained.

5. A measure of renal volume and split renal function from contrast-enhanced CT can be acquired by means of an approximation formula with sufficient accuracy for routine purposes.

6. Split renal function calculated from contrast-enhanced CT gives equivalent results irrespective of scanning in corticomedullary or nephrographic contrast phase.

Implications in the living kidney donor perspective

Living renal donation is an exceptional clinical situation, as already observed – and an exceptionally complex one. Several variables are included in the overall evaluation ending up in the eventual qualification of the donor and selection of kidney. The principal challenge is to make an extrapolation of the expected long-term outcome for the donor, based on present data. Age (and life expectancy) and comorbidity are vital parameters for the estimation of the GFR required for donation.

A predicted creatinine clearance of 40 mL/min/1.73 m² at the age of 80 years has been suggested as a minimum, although that may be stretched to 30 mL/min/1.73 m² for an individual informed of the interventions possibly needed to maintain expected quality of life [58]. A normal physiological decline in GFR of 1 mL/min/1.73 m² per year from the age of 40 is included in the calculus. However, after donor nephrectomy, a rapid adaptation occurs due to hyperfiltration of the remaining kidney, resulting in a decrease in GFR of approximately 25%
(rather than 50%). Data demonstrates that this level remains stable for up to 10 years, thus compensating for the expected normal ageing effects [59]. Even for longer follow-up times, no significantly accelerated loss of renal function has been observed, indicating the absence of a deleterious effects of the hyperfiltration [60].

In summary, the ideal living renal donor is younger than 65 years, has a creatinine clearance ≥ 80 mL/min/1.73 m² and normal body habitus, blood pressure, glucose tolerance and urinalysis [61]. Under those conditions, the residual capacity is large enough to compensate for a minor side difference in renal function, should it be at hand. If any of the stated criteria is missing, or if exceptional circumstances are present in the recipient, the complexity of the situation immediately calls for an individual judgment. Further increasing the intricacy is a report on the poor correlation and reproducibility of currently used measures of renal function [62].

A final verdict concerning the “truth” of split renal function is not present, based on the current findings. Moreover, no exact definition of what deviation from ⁹⁹ᵐTc-MAG3 renography is allowed with CT is given. This is caused partly by the circumstance discussed above, concerning the situation-specific factors of the donor investigation, and partly by the examples of questioned accuracy of renography previously observed. The question of whether this is a problem big enough to activate further investigations against a gold standard will be negatively answered. In the perspective of previously published results, this study gives sufficient evidence to suggest an adjustment in the protocol for donor investigation. In an uncomplicated situation, primary estimation of split renal function should be made from the routinely performed CT. Corticomedullary or nephrographic contrast phase can be utilized and a semi-automatic method is recommended where available, or as an alternative, the approximation method. Background correction should be made from unenhanced scans or with a standardized value of renal parenchyma unless such are included. In case of uncertainty, further investigation with gamma camera renography is suggested. The main indication for such secondary examination would be an abnormal value of split renal function with CT, unexplained by a difference in the kidneys’ volumes. Furthermore, the threshold for complement with gamma camera renography would be lower in selected delicate cases, e.g. when plasma clearance indicates borderline values in the donor or when other complicating factors are present.
Conclusions in a wider perspective

Although specific in many respects, the anatomy or physiology of living kidney donors is not unique. Several other clinical situations occur when split renal function is asked for, to which the present discussion can be transferred. Examples include investigation of an individual with a renal tumour planned for either nephrectomy or nephron-sparing surgery, or a person with symptoms originating from a poorly functioning kidney which may be relieved by nephrectomy. In both of those situations, a contrast-enhanced CT is likely to be planned or at hand for the clinical evaluation. From the present conclusion, it follows that such a CT examination, if performed with a proper protocol, can be used for the estimation of split renal function as well. Similar precautions apply concerning when to perform additional renography for secondary evaluation. For isolated knowledge of split renal function or repeated follow-up, CT is inadvisable due to the higher radiation dose compared to $^{99m}$Tc-MAG3 renography.

In situations of acute disorders of the kidneys, the alternative methods have not been studied and at present cannot be recommended. Hypothetically, CT calculation from nephrographic phase would be preferable, as the normal association of perfusion and filtration may be altered in an acute state. In situations where careful characterization of accessory arteries is not as crucial as in the donor investigation, MRI can be recommended, although a dedicated scanning for the specific purpose is required in that case. Finally, a further perspective concerning the measurement with CT includes evaluation of scanners with dual source technology, which can render a separate unenhanced phase for background correction unnecessary.
Sammanfattning på svenska


Syftet med den här studien har varit att undersöka möjligheten att få information om separat njurfunktion från CT-undersökningen. Om så är fallet skulle utredningen av en blivande njurdonator kunna förenklas ytterligare, till en enda kombinerad anatomisk och funktionell undersökning. Sedan tidigare finns några olika beskrivningar av metoder som skulle kunna möjliggöra detta, men utan att någon standard har etablerats. Ett problem vid utvärdering med renografi som referens är att inte heller den metoden säkert kan sägas representera ”sanningen” om separat njurfunktion.
I det första delarbetet analyserades CT-undersökningar av 27 tidigare presumtiva njurdonatorer. I bild materialet uppmättes den totala mängden kontrastmedel i respektive njure, vilken är beroende av njurens storlek och genomsnittliga tätethetsvärde och antas vara proportionell mot njurens funktion. Andelen för respektive njure angavs i procent och resultatet jämfördes med motsvarande resultat från den renografi som samtliga personer också genomgått. Resultatet visade att det fanns en potential hos CT för bestämning av separat njurfunktion. En teknisk begränsning orsakad av att CT-utrustningen var för långsam försvårade dock bedömningsen. Dessutom hade samtliga undersökta personer värden på separat njurfunktion som låg inom normala gränser, varför slutsatser om den diagnostiska träffsäkerheten hos CT var svåra att dra.

I delarbete två genomfördes en liknande jämförelse mellan CT och renografi i ett material av 38 patienter som undersöks för misstänkt kärlsjukdom i njurarerna, varför en större spridning i separat njurfunktion förväntades. I detta material användes dessutom en modernare, och därmed snabbare, CT-utrustning som förväntades korrigera det fel som noterats i delarbete ett. Parallellt utvärderades en automatiserad metod att utföra beräkningarna utifrån CT-materialet i detta delarbete. Studien visade att förmågan hos CT att detektera sidoskillnader i separat njurfunktion motsvarade den hos renografi, men att det i vissa fall förelåg en metodskillnad utöver den önskvärda. Det visades också att den automatiserade mätmetoden gav resultat som var jämförbara med den tidigare använda, manuella metoden.

För att ytterligare belysa metodskillnader gjordes i delarbete tre en undersökning med en tredje metod för att mäta separat njurfunktion. Med hjälp av kontrastförstärkt magnetisk resonanstomografi (MRT) kunde njurarernas förmåga till upptag och utsöndring av kontrastmedel bedömas och kvantifieras. För att underlätta en undersökning över flera minuter användes en dittills oprövd metod att synkronisera bildtagningen med andningen. Hos 26 patienter jämfördes resultaten från MRT med renografi. I en mindre grupp om 16 patienter kunde även jämförelse mellan MRT och CT göras. Dessa jämförelser indikerade att samtliga tre metoder i de flesta fall gav likvärdiga resultat, men att enstaka fall förekom där någon av metoderna avvek från de två övriga. Någon systematisk avvikelse sågs dock inte, och slutsatsen blev att undersökningarna var väsentligen jämförbara.
I det fjärde delarbetet undersöks huruvida en enklare mätmetod kunde ge tillförlitliga värden på separatfunktion. Sextiofyra patienter som genomgick CT av njurarna inkluderades i denna studie. En formel för uppskattning av njurvolym tillämpades som ett sätt att undgå mätning i vart och ett av det stora antal snitt som en CT-undersökning består av. Dessutom utvärderades vilken betydelse tidpunkten efter kontrastinjektion hade för resultaten av separat njurfunktion med CT. Detta är en faktor som är betydelsefull vid planeringen av CT-undersökningen för att ge bästa diagnostiska underlag i relation till den tillförda stråldosen. Jämförelserna visade att det i de allra flesta fall ger tillräcklig exakthet att använda en formel för uppskattning, om det inte föreligger en avvikelse i någon av njurarnas form. Dessutom demonstrerades att resultaten blir likvärdiga oavsett om undersökningen är gjord omedelbart efter kontrastmedelsinjektion, eller vid en något senare tidpunkt.

Den sammantagna slutsatsen blir att det befintliga bildmaterialet från en CT-undersökning kan användas för att bestämma separat njurfunktion hos en levande njurdonator med en exakthet som i normalfallet är tillräcklig. Avvikelser från resultaten vid renografi kan i vissa individuella fall hänföras till osäkerhet i endera metoden och någon oomtvistlig referensmetod finns inte tillgänglig – två icke validerade metoder för beräkning av separat njurfunktion, renografi och CT, jämförs med varandra. Vid tveksamhet utifrån resultatet som uppnås med CT kan därför renografi utföras som en sekundär undersökning för starkare beslutsunderlag. Den förändring i rutinutredningen av levande njurdonatorer som föreslås minskar strålningsexponeringen och utredningsbördan för den enskilda individen.
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